PATENT COOPERATION TREATY

DATE OF DEPOSIT: February 28, 2006

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

DOCKETED FOR: 7/15/05

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/028004	27.08.2004	29.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/30, C07K16/46, A61K39/395, A61P35/00, G01N33/574, G01N33/577, A61K51/10, C12N15/13,

Applicant
NATIONAL INSTITUTES OF HEALTH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Nooij, F Telephone No. +31 70 340-3267

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/028004

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/028004

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 28, 29, 35 (all partially)

because:

☒ the said international application, or the said claims Nos. 28,29,35 (all partially, for reasons of industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/028004

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	20-23,30-36,38-43
	No:	Claims	1-19,24-29,37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-43
Industrial applicability (IA)	Yes:	Claims	1-27,30-34,36-43
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/028004

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 28, 29 and 35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are cited in this communication:

D1: N. GONZALES ET AL.: "Reducing the potential immunogenicity of humanized CC49 by genetic manipulation of framework residues." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. ANNUAL MEETING, vol. 44, July 2003 (2003-07), page 1118, USA

D2: R. DE PASCALIS ET AL.: "Generation of minimally immunogenic high affinity variants of humanized anti-carcinoma antibody HuCC49V10 by in vitro affinity maturation." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. ANNUAL MEETING, vol. 44, July 2003 (2003-07), pages 1115-1116, XP001204653 USA

D3: M. TAMURA ET AL.: "Structural correlates of an anticarcinoma antibody: Identification of specificity-determining residues (SDRs) and development of a minimally immunogenic antibody variant by retention of SDRs only." THE JOURNAL OF IMMUNOLOGY, vol. 164, no. 3, 1 February 2000 (2000-02-01), pages 1432-1441, XP000901556 BALTIMORE, MD, USA

D4: WO 00/26394 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 11 May 2000 (2000-05-11)

D5: S. KASHMIRI ET AL.: "Generation, characterization and in vivo studies of humanized anticarcinoma antibody CC49." HYBRIDOMA, vol. 14, no. 5, 1995, pages 461-473,

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/028004

XP000198397 NEW YORK, NY, USA
D6: US-B1-6 495 137 (MEZES ET AL.) 17 December 2002 (2002-12-17)

1. NOVELTY (Article 33(2) PCT)

1.1 Document *D1* discloses an array of HuCC49V10 variants that were generated by replacing the murine residues that were retained in the humanized antibody with their counterparts in the human template (LEN for V_L and 21/28'CL for V_H). One example is specifically mentionned: V59 contains only 3 murine residues in its V_L and V_H frameworks compared to 19 in the parental HuCC49V10 antibody. Said variant has a slightly higher affinity for the TAG-72 antigen and a lower immunogenicity than said HuCC49V10 antibody, and may be used therapeutically against human carcinomas.

1.2 In view of the prior art cited, present claims **1-19, 24-29** and **37** are deemed to be **not novel**. Present claims **20-23, 30-36** and **38-43** appear to be novel and therefore fulfill the requirements of Article 33(2) PCT.

2. INVENTIVE STEP (Article 33(3) PCT)

2.1 Present claims **20-23, 30-36** and **38-43** ultimately refer back to the humanized antibody of present claim **1**. Said antibody is, however, deemed to be not novel and not inventive. The provision of antibodies linked to labels, effector molecules, kits with instructions, encoding nucleic acids, vectors and host cells is well known in the art and does not involve an inventive step. The diagnostic use of anti-TAG-72 antibodies, based on CC49, has been disclosed in the prior art (see *D1-D6*). Substitutions as claimed in present claims **42** and **43** have been disclosed for the variants as disclosed in *D2*.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

3.1 For the assessment of the present claims **28, 29** and **35** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to

the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

4. CLARITY/SUPPORT (Article 6 PCT)

4.1 According to present claim **1**, L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2 and H-CDR3 are all derived from HuCC49V10. Since the SEQ ID Nos 9-14 all refer to the CDRs of HuCC49V10, present claims **8** and **9**, which both refer back to said claim **1**, are superfluous and do not fulfill the requirements of Article 6 PCT with regard to conciseness.

4.2 Present claim **18** is unclear and not supported by the description in the sense of Article 6 PCT: Clear and supported would be
i) the residue at position 67 in the heavy chain is **valine**, or
ii) the position at which isoleucine is, is position **69**.

4.3 Present claim **37** refers to light-chain CDRs comprising amino acid sequences set forth in SEQ Nos 9-**12**. Since SEQ ID NO. 12 contains the amino acid sequence of CDR1 of the **heavy** chain of HuCC49V10, present claim **37** is unclear in the sense of Article 6 PCT.

4.4 Present claims **26, 29** and **33** refer to **nucleic acids** deposited as ATCC PTA-5415, instead of to **hybridomas** with such a deposit number, thereby rendering the definition of the subject-matter of said claims unclear in the sense of Article 6 PCT. The applicant is reminded that should he enter into the regional phase for the EPO, in order to comply with the provisions of the EPC, the applicant should provide the Examining Division with the deposit receipt or any other proof of availability of a microorganism (e.g. hybridoma) with the deposit number ATCC PTA-5415 according to present claims **26, 29** and **33**.

EXPRESS MAIL LABEL NO. EV669611737US
DATE OF DEPOSIT: February 28, 2006

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International application No.

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